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(54) Title: ANHYDROUS CRYSTALLINE FORM OF VALACYCLOVIR HYDROCHLORIDE

(57) Abstract: Valacyclovir hydrochloride in anhydrous crystalline form having substantially the following d-spacing pattern (in angstroms) (see (I)).

d-spacing
6.76
9.36
11.54
13.98
15.45
15.75
17.12
19.10
21.39
23.02
24.23
26.41
27.46
28.06

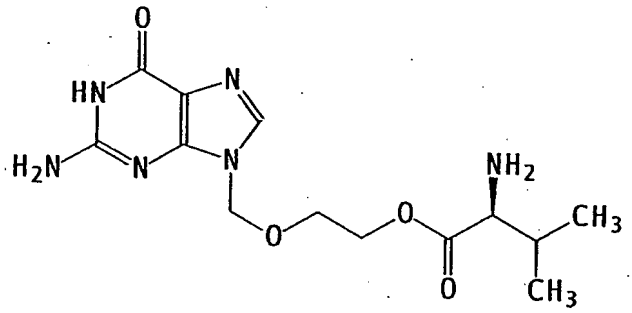
WO 2004/052892 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ANHYDROUS CRYSTALLINE FORM OF VALACYCLOVIR HYDROCHLORIDE

The present invention relates to an anhydrous crystalline form of valacyclovir hydrochloride and to its uses and processes for the production thereof.

Valacyclovir is an L-valine ester with 9-[(2-hydroxyethoxy)methyl]guanine. It has the structure shown below



The preparation of valacyclovir is known and is described in, for example, US Patent No. 4957924 and its hydrochloride, which normally occurs as a hydrate, is now widely used as an antiviral agent, especially in the treatment of herpes viruses. Valacyclovir is a prodrug of acyclovir and hence has similar adverse effects, however, valacyclovir is a more bioavailable drug than its counterpart acyclovir and is absorbed more readily in the gastrointestinal tract following oral administration. Whilst valacyclovir hydrochloride is normally administered as a hydrate, it has been found to exist in other forms.

In US 6,107,302 an anhydrous crystalline form of valacyclovir hydrochloride is described which is prepared by contacting valacyclovir hydrochloride with 15 to 40% w/w of a lower alcohol or ketone. The resulting anhydrous crystalline valacyclovir

hydrochloride is characterised by its X-ray diffraction spectrum having characteristic d-spacing as follows: approximately 24.8, 10.25, 8.14, 7.31, 6.41, 5.85, 5.38, 5.24, 4.89, 4.43, 4.07, 3.71, 3.40, 3.31, 2.92 and 2.78 angstroms.

Hence, the hydrochloride form in US 6,107,302 has distinctive peaks at diffraction angles 2θ= approximately 8.62, 10.86, 12.12, 14.50 and 23.95°.

The present inventors have surprisingly found a new anhydrous crystalline form of valacyclovir hydrochloride which differs from those known in the prior art and which exhibits excellent stability both at room and elevated temperatures.

Hence, viewed from one aspect the invention provides valacyclovir hydrochloride in anhydrous crystalline form having substantially the following d-spacing pattern (in angstroms):

d-spacing
6.76
9.36
11.54
13.98
15.45
15.75
17.12
19.10
21.39
23.02
24.23
26.41
27.46
28.06

Viewed from another aspect the invention provides a

pharmaceutical composition comprising a valacyclovir hydrochloride form as hereinbefore described along with one or more pharmaceutical carriers/excipients.

Viewed from another aspect the invention provides a valacyclovir hydrochloride form as hereinbefore described for use in medicine, e.g. as an antiviral agent.

Viewed from a still yet further aspect the invention provides the use of a valacyclovir hydrochloride form as hereinbefore described in the manufacture of a medicament for use as an antiviral agent.

By anhydrous crystalline form according to the invention is meant a crystalline form having substantially the same X-ray powder diffraction pattern as hereinbefore described and shown in Figure 2. The valacyclovir hydrochloride form should be substantially free of any waters of hydration. The water content of the valacyclovir hydrochloride form of the invention should be below 1.5%, preferably below 1%, for example between 0.5% and 1%, e.g. 0.9% by weight. Water content can be measured using standard Karl-Fischer apparatus (e.g. as described in the 1990 US Pharmacopoeia at pages 1619-1621).

The infrared spectrum of the valacyclovir hydrochloride form of the invention should preferably be substantially as described below:

(the underlined peaks are considered the most characteristic of the anhydrous crystalline form of the invention)

IR (cm^{-1}): 3377.99, 3285.87, 3197.62, 2930.92, 1749.72, <u>1686.42</u>, 1631.12, 1607.17, <u>1572.60</u>, <u>1533.52</u>, 1476.48, 1364.98, 1298.63, 1258.79, 1248.27, 1225.22, 1132.81, 1097.06, 778.37, 759.33.

The person skilled in the art will appreciate that wavenumber measurements may vary slightly on different acquisitions or from machine to machine. Hence, the IR spectrum of the valacyclovir hydrochloride form of the invention should be substantially as described above, i.e. wavenumbers should be within 1% of the given values, preferably within 0.5% of the given values.

Thus, viewed from a further aspect the invention provides valacyclovir hydrochloride in anhydrous crystalline form having substantially the characteristic infrared peaks described above.

The X-ray diffraction pattern of the valacyclovir hydrochloride form may have substantially the following peaks (intensities may vary due to preferred orientation).

d-spacing	Rel. Int %
6.76	79.7
9.36	100.0
11.54	21.1
13.98	23.7
15.45	23.5
15.75	57.4
17.12	59.0
19.10	38.7
21.39	46.4
23.02	39.7
24.23	20.6
26.41	46.4
27.46	55.5
28.06	47.8

X-ray diffraction measurements should be taken using a standard Kα1 (Cu λ=1.5406 angstroms) radiation. Full details of the apparatus used may be found in the

experimental section.

The person skilled in the art will appreciate that d-spacing measurements may vary slightly on different acquisitions or from machine to machine. Hence, the d-spacing measurements of the valacyclovir hydrochloride form of the invention should be substantially as described above, i.e. d-spacing figures should be within 1% of the given values, preferably within 0.5 % of the given values.

The new anhydrous crystalline forms of the invention may be prepared from hydrated valacyclovir hydrochloride. Such a hydrate should be suspended in a lower alcohol, e.g. C_{1-6}-alcohol, preferably C_{1-4}-alcohol, especially ethanol which is substantially pure, i.e. substantially free of any other solvent or water. Preferably therefore, the solvent should be at least 99% lower alcohol, especially 99.8% lower alcohol, e.g. absolute ethanol.

The lower alcohol/hydrochloride mixture should then be heated at elevated temperature e.g. between 50-70°C, preferably 60°C for at least 12 hours, preferably 15-24 hours, e.g. 20-21 hours. The solvent may then be evaporated under reduced pressure, for example at 60°C and the crystalline solid thus obtained is valacyclovir hydrochloride as the new anhydrous crystalline form of the invention.

In an alternative embodiment the suspension of lower alcohol and valacyclovir hydrochloride in hydrated form may be added to refluxing lower alcohol, e.g. over 30 minutes. The refluxing alcohol should also be substantially pure as described above. Approximately one third of the solvent is then distilled off and the resulting suspension kept at room temperature, e.g. 20-25°C for at least 8 hours, e.g. 8-16 hours. The resulting solid may be filtered and washed with substantially pure lower alcohol, e.g. absolute ethanol and dried, e.g. under vacuum at 60°C. An anhydrous

crystalline form of valacyclovir hydrochloride of the invention is formed.

Once a seed crystal of valacyclovir hydrochloride in anhydrous crystalline form as claimed herein has been formed it is possible to produce more valacyclovir hydrochloride form of the invention using seeding techniques. For example, valacyclovir hydrochloride dihydrate can be suspended in substantially pure lower alcohol, e.g. isopropanol or isobutanol, and seeded with the anhydrous crystalline form. The suspension should be refluxed for a number of hours and filtered whilst still hot. After drying, the resulting solid is the anhydrous crystalline form of the invention.

Hence, viewed from a still yet further aspect the invention provides a process for the preparation of valacyclovir hydrochloride in anhydrous crystalline form having the X-ray diffraction pattern as hereinbefore described comprising;

1) mixing valacyclovir hydrochloride hydrate with a substantially pure C_{1-6} lower alcohol solvent and heating the resulting suspension;

2) evaporating the solvent under reduced pressure and isolating the resulting solid.

Alternatively, the invention provides a process for the preparation of valacyclovir hydrochloride in anhydrous crystalline form having the X-ray diffraction pattern as hereinbefore described comprising;

1) mixing valacyclovir hydrochloride hydrate with a substantially pure C_{1-6} lower alcohol solvent and adding the resulting suspension to substantially pure refluxing lower alcohol;

2) distilling off the solvent to form a suspension and maintaining the same at room temperature for at least 8 hours; and

3) isolating the resulting solid.

The valacyclovir hydrochloride forms of the invention exhibit remarkable stability and have been

shown to be stable at room temperature for over 3 years. Such stability is vital for a pharmaceutical since stocks thereof may be stored for long periods prior to use. Moreover, when heated at 100°C, the new form of valacyclovir hydrochloride exhibits stability for over 550 hours. The valacyclovir hydrochloride form of the invention therefore also shows surprising heat stability, again a property of critical importance to a pharmaceutical. The forms of the invention are therefore suitable for transport in countries where ambient temperatures are exceptionally high.

The valacyclovir hydrochloride form described above may be formulated and employed in medical treatment as is well known in the art. For example, valacyclovir hydrochloride may be employed as an antiviral agent especially in the treatment of diseases caused by various DNA viruses, such as herpes infections, for example, herpes simplex I and II, varicella zoster, cytomegalovirus, Epstein-Barr viruses or human herpes virus-6 as well as diseases caused by hepatitis B. The active compound can also be used for the treatment of papilloma or wart virus infections and may therefore be administered in combination with other therapeutic agents for example with zidovudine, to treat retroviral associated infections in particular HIV infection.

Pharmaceutical preparations may take the form of, *inter alia*, tablets, capsules, powders, solutions, suspensions or emulsions and they be formulated using standard techniques. While any administration route is possible the preferred route of administration is orally. The new valacyclovir hydrochloride form of the invention may be administered alone or in combination with other forms of valacyclovir hydrochloride or together with any other active ingredients. The amount of valacyclovir hydrochloride administered will vary depending on the patient but will be readily determined by the person skilled in the art. Dosage regimes are

known.

The invention will now be described further with reference to the following non-limiting examples and figures.

Figure 1 is the infrared spectrum of the valacyclovir hydrochloride form of the invention produced in Example 1;

Figure 2 is the X-ray diffraction spectrum of the valacyclovir hydrochloride form of the invention produced in Example 1.

Example 1

3g of valacyclovir hydrochloride (hydrated form) was suspended in 8 ml of ethanol 99.8% and heated at 60°C for 20-21 hours. The solvent was evaporated at 60°C under reduced pressure and the crystalline solid thus obtained was characterised as a new anhydrous crystalline form of valacyclovir hydrochloride.

Nicolet Avatar 320 (FT-IR)

IR (cm^{-1}): 3377.99, 3285.87, 3197.62, 2930.92, 1749.72, 1686.42, 1631.12, 1607.17, 1572.60, 1533.52, 1476.48, 1397.59, 1364.98, 1342.17, 1298.63, 1258.79, 1248.27, 1225.22, 1191.99, 1151.67, 1132.81, 1097.06, 1042.51, 1017.65, 868.28, 829.01, 778.37, 759.33, 729.45, 700.52, 688.32, 631.20.

XRD:

Diffractometer: PW1710 BASED
Tube Anode: Cu
Generator tension [kV]: 40
Generator current [mA]: 40
Wavelength alpha 1: 1.54060
Wavelength alpha 2: 1.54439
Intensity ratio alpha 2/alpha 1: 0.500
Divergence slit:1.5
Receiving slit: 0.2
Monochromator used: Yes

Start angle [0.52θ]: 5.000
End angle [0.52θ]: 60.000
Step [0.52θ]: 0.2
Maximum intensity: 1536.640
Time per step [s]: 1.000

Peak positions defined by: Minimum of 2nd derivative peak
Minimum peak tip width: 0.00
Maximum peak tip width: 1.00
Peak base width: 2.00
Minimum significance: 0.75
No. of peaks: 47

Data:

Angle [½2Õ]	d-value Á1 []	d-value Á2 []	Peak width [½2Õ]	Peak int [counts]	Back. int [counts]	Rel. int [%]	Signif
6.765	13.0556	13.0877	0.140	1225	98	79.7	10.2
8.160	10.8265	10.8532	0.200	61	81	4.0	1.5
9.360	9.4410	9.4643	0.140	1537	77	100.0	12.4
11.540	7.6620	7.6808	0.140	324	71	21.1	4.6
13.455	6.5755	6.5917	0.080	193	67	12.6	0.8
13.980	6.3297	6.3453	0.140	365	67	23.7	4.5
15.445	5.7325	5.7466	0.120	361	67	23.5	1.5
15.750	5.6221	5.6360	0.180	882	67	57.4	12.3
16.305	5.4320	5.4453	0.100	292	67	19.0	1.2
17.125	5.1737	5.1864	0.180	906	67	59.0	12.0
18.640	4.7565	4.7682	0.120	225	67	14.6	1.3
19.105	4.6417	4.6531	0.120	595	67	38.7	2.1
19.780	4.4848	4.4959	0.100	269	67	17.5	1.3
20.135	4.4065	4.4174	0.120	108	67	7.0	0.9
20.740	4.2793	4.2899	0.060	210	67	13.7	1.0
21.390	4.1508	4.1610	0.140	713	67	46.4	4.1
22.525	3.9441	3.9538	0.100	299	66	19.5	0.8
23.025	3.8596	3.8691	0.060	610	66	39.7	2.7
24.235	3.6695	3.6786	0.120	317	66	20.6	2.1
24.795	3.5879	3.5967	0.100	79	66	5.2	0.9
25.525	3.4869	3.4955	0.200	243	66	15.8	3.0
26.415	3.3714	3.3797	0.140	713	66	46.4	4.2
27.460	3.2455	3.2534	0.100	853	66	55.5	1.7
28.060	3.1774	3.1852	0.200	734	66	47.8	8.24
28.875	3.0896	3.0972	0.200	182	66	11.9	2.16
29.350	3.0406	3.0481	0.160	117	66	7.6	0.90
30.195	2.9574	2.9647	0.160	166	64	10.8	0.99
31.045	2.8784	2.8855	0.100	282	64	18.4	1.16
31.950	2.7989	2.8058	0.200	164	64	10.7	1.77
32.620	2.7429	2.7496	0.100	185	64	12.0	0.79
33.470	2.6752	2.6817	0.320	72	64	4.7	1.19
34.915	2.5677	2.5740	0.200	190	64	12.4	2.19
35.340	2.5378	2.5440	0.160	204	64	13.3	1.43
35.945	2.4964	2.5026	0.240	151	64	9.8	1.48
38.940	2.3110	2.3167	0.480	37	62	2.4	1.18
40.805	2.2096	2.2150	0.120	81	62	5.3	0.81
41.440	2.1772	2.1826	0.160	56	62	3.7	0.84
41.905	2.1541	2.1594	0.160	81	62	5.3	1.11
43.085	2.0978	2.1030	0.200	102	62	6.6	1.46
43.920	2.0599	2.0649	0.240	44	62	2.8	0.77
46.115	1.9668	1.9716	0.240	41	62	2.7	1.09
48.055	1.8918	1.8965	0.240	29	61	1.9	0.87
48.895	1.8613	1.8658	0.400	28	61	1.8	0.78
51.665	1.7678	1.7721	0.640	21	61	1.4	0.93
53.715	1.7051	1.7093	0.240	22	61	1.4	1.02
54.800	1.6738	1.6780	0.320	21	61	1.4	0.86
56.740	1.6211	1.6251	0.480	12	59	0.8	1.25

Example 2

Valacyclovir hydrochloride (hydrated form) was suspended in ethanol 99.8%. The suspension was added over about 30 minutes to refluxing ethanol 99.8%. The solvent was distilled off and the suspension kept at 20-25°c for 12 hours. The solid was filtered, washed twice with absolute ethanol and dried under vacuum at 60°C. The crystalline solid thus obtained was characterised as a new anhydrous crystalline form of valacyclovir hydrochloride.

Example 3

10g of valacyclovir hydrochloride dihydrate (KF 6%) was suspended in 100 ml of isopropanol 99% and seeded with 50 mg of anhydrous crystalline valacyclovir hydrochloride. The suspension was refluxed for 5 hours and filtered hot. The solid was dried at 110°C for 10 hours (yield = 7.52g).

Example 4

10g of valacyclovir hydrochloride dihydrate (KF 6%) was suspended in 100 ml of isobutanol 99% and seeded with 50 mg of anhydrous crystalline valacyclovir hydrochloride. The suspension was refluxed for 5 hours and filtered hot. The solid was dried at 110°C for 10 hours (yield = 8.24g).

Claims

1. Valacyclovir hydrochloride in anhydrous crystalline form having substantially the following d-spacing pattern (in angstroms):

d-spacing
6.76
9.36
11.54
13.98
15.45
15.75
17.12
19.10
21.39
23.02
24.23
26.41
27.46
28.06

2. Valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 having substantially the X-ray diffraction pattern of Figure 2.

3. Valacyclovir hydrochloride in anhydrous crystalline form having substantially the characteristic infrared peaks

IR (cm^{-1}): 1686.42, 1572.60, 1533.52.

4. Valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 3 having substantially the characteristic infrared peaks

IR (cm^{-1}): 3377.99, 3285.87, 3197.62, 2930.92, 1749.72, 1686.42, 1631.12, 1607.17, 1572.60, 1533.52, 1476.48, 1364.98, 1298.63, 1258.79, 1248.27, 1225.22, 1132.81, 1097.06, 778.37, 759.33.

5. Valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 3 having substantially the infra-red absorption spectrum of Figure 1.

6. A pharmaceutical composition comprising a valacyclovir hydrochloride form as claimed in claim 1 to 5 along with one or more pharmaceutical carriers/ excipients.

7. Valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 to 5 for use in medicine.

8. Use of valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 to 5 in the manufacture of a medicament for use as an antiviral agent.

9. A process for the preparation of valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 to 5 comprising;

1) mixing valacyclovir hydrochloride hydrate with a substantially pure C_{1-6} lower alcohol solvent and heating the resulting suspension;

2) evaporating the solvent under reduced pressure and isolating the resulting solid.

10. The process of claim 9 wherein said solvent is ethanol.

11. The process of claim 9 or 10 wherein the suspension is heated at between 50 to 70°C for at least 12 hours.

12. The process of claim 11 wherein the suspension is heated at 60°C for 20-21 hours.

13. A process for the preparation of valacyclovir hydrochloride in anhydrous crystalline form as claimed in claim 1 to 5 comprising;

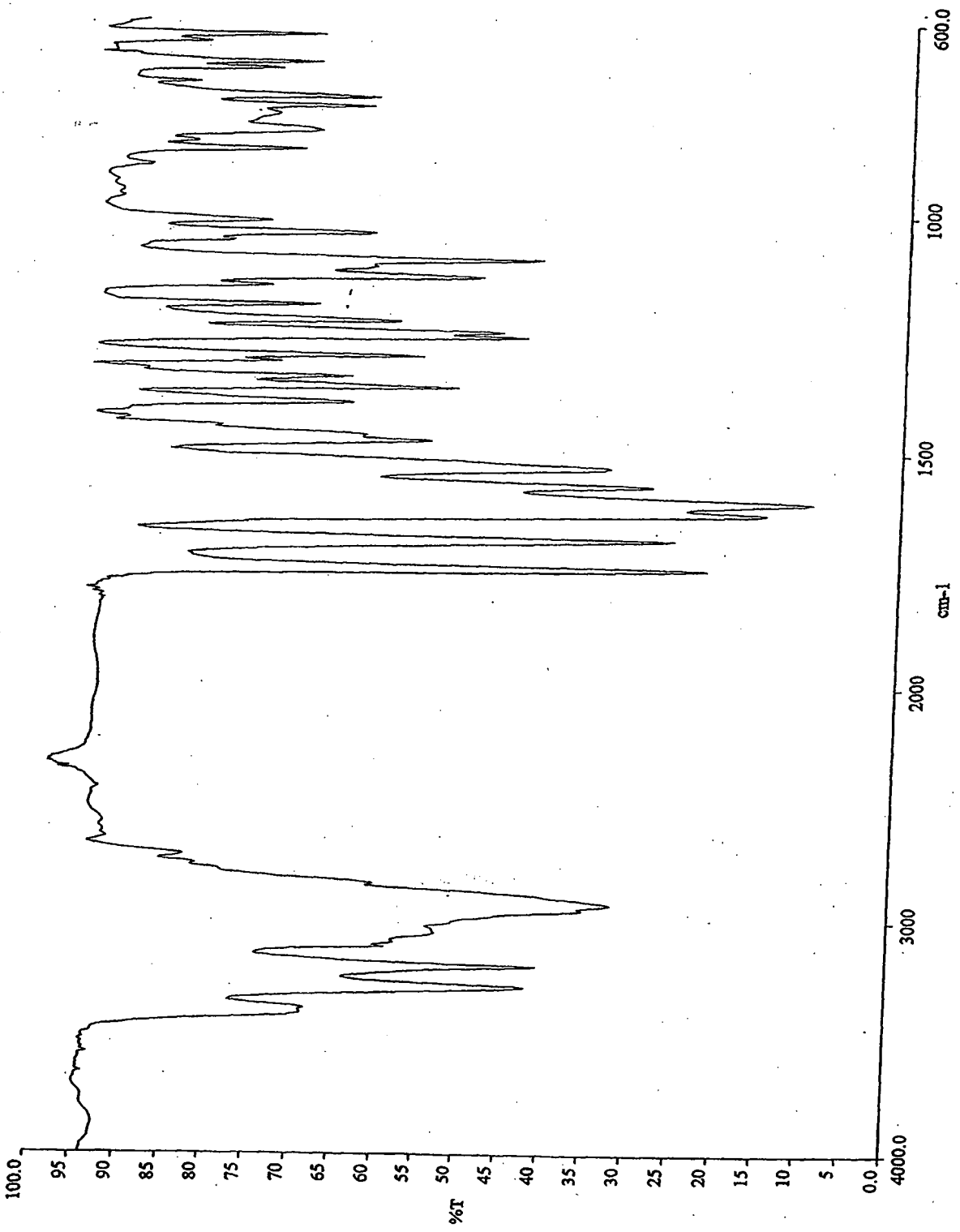
1) mixing valacyclovir hydrochloride hydrate with a substantially pure C_{1-6} lower alcohol solvent and adding the resulting suspension to substantially pure refluxing lower alcohol;

2) distilling off the solvent to form a suspension and maintaining the same at room temperature for at least 8 hours; and

3) isolating the resulting solid.

14. The process of claim 13 wherein the solvent and refluxing lower alcohol are ethanol.

15. The process of claim 13 or 14 wherein approximately one third of the solvent is distilled off to form said suspension.


100.0
95
90
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45
40
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20
15
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0.0
%T
4000.0
3000
2000
1500
1000
600.0
cm-1

Figure 1

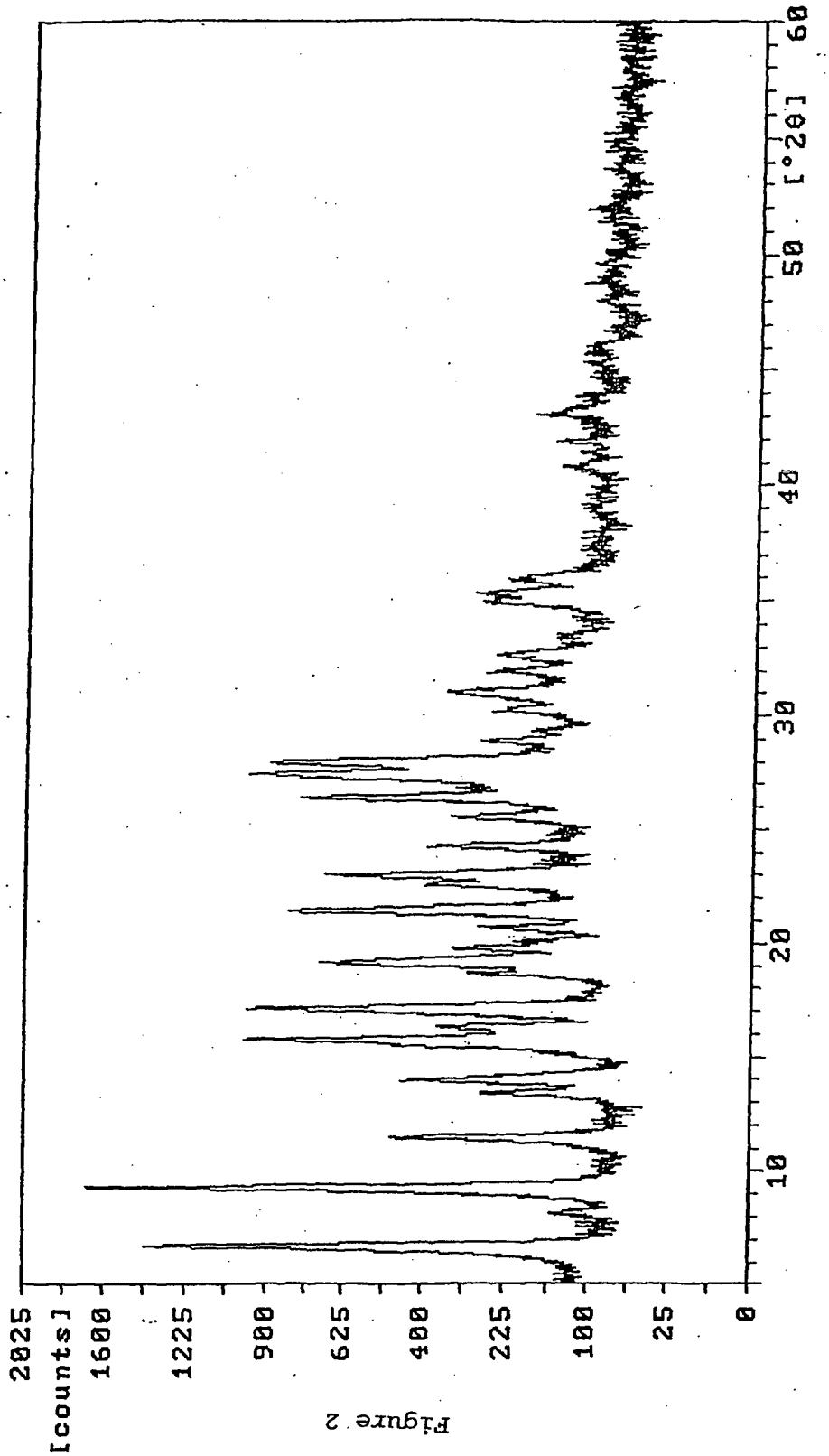
2025
[counts]
1600
1225
900
625
400
225
100
25
0
10
20
30
40
50
60
[°2θ]

Figure 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/13951

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/18 A61K31/522 A61P31/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 976 750 A (AJINOMOTO KK) 2 February 2000 (2000-02-02) claims; figures 1,2; examples	1-15
Y	US 6 107 302 A (SKINNER DAVID MICHAEL ET AL) 22 August 2000 (2000-08-22) cited in the application claims; figures; examples	1-15
P,Y	WO 03 040145 A (FAIN HELENE S ;LAKE PHILIP G (GB); GLAXO GROUP LTD (GB); JONES DAV) 15 May 2003 (2003-05-15) page 13 -page 15; claims; figures 1-10; examples	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2004	22/03/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/13951

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 957 924 A (BEAUCHAMP LILIA M) 18 September 1990 (1990-09-18) cited in the application the whole document	1-15
P,A	WO 03 041647 A (DOLITZKI BEN ZION ;ETINGER MARINA YU (IL); NISNEVICH GENNADY A (IL) 22 May 2003 (2003-05-22) claims	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/13951

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0976750 A	02-02-2000	AU 5495898 A	07-08-1998
		CA 2278474 A1	23-07-1998
		EP 0976750 A1	02-02-2000
		CN 1250449 T	12-04-2000
		WO 9831683 A1	23-07-1998
US 6107302 A	22-08-2000	AP 662 A	19-08-1998
		AU 702794 B2	04-03-1999
		AU 4453996 A	07-08-1996
		BG 63393 B1	31-12-2001
		BG 101833 A	30-04-1998
		BR 9606768 A	30-12-1997
		CA 2210799 A1	25-07-1996
		CN 1179159 A ,B	15-04-1998
		CZ 9702294 A3	17-12-1997
		EA 364 B1	24-06-1999
		EE 9700175 A	16-02-1998
		EP 0804436 A1	05-11-1997
		FI 973063 A	18-09-1997
		WO 9622291 A1	25-07-1996
		HR 960024 A1	31-10-1997
		HU 9801836 A2	28-05-1999
		IL 116831 A	30-10-1998
		IN 182468 A1	17-04-1999
		JP 3176633 B2	18-06-2001
		JP 11503718 T	30-03-1999
		NO 973326 A	16-09-1997
		NZ 298851 A	28-01-1999
		OA 10499 A	10-04-2002
		PL 321326 A1	08-12-1997
		RO 118693 B1	30-09-2003
		SK 96597 A3	04-02-1998
		TR 9700656 T1	21-03-1998
		ZA 9600449 A	07-08-1996
WO 03040145 A	15-05-2003	FR 2831885 A1	09-05-2003
		GB 2383038 A	18-06-2003
		GR 2002100478 A	16-07-2003
		WO 03040145 A1	15-05-2003
US 4957924 A	18-09-1990	AP 55 A	26-09-1989
		AP 160 A	18-11-1991
		AT 116648 T	15-01-1995
		AT 138660 T	15-06-1996
		AU 612393 B2	11-07-1991
		AU 2097888 A	16-02-1989
		CA 1340083 C	13-10-1998
		CN 1032538 A ,B	26-04-1989
		CS 8805594 A2	13-06-1990
		CY 1833 A	01-12-1995
		DD 282229 A5	05-09-1990
		DE 3852682 D1	16-02-1995
		DE 3852682 T2	22-06-1995
		DE 3855333 D1	04-07-1996
		DE 3855333 T2	05-12-1996
		DK 82694 A	08-07-1994
		DK 170045 B1	08-05-1995
		EP 0308065 A2	22-03-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/13951

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4957924 A		EP 0596542 A1	11-05-1994
		ES 2065914 T3	01-03-1995
		ES 2087639 T3	16-07-1996
		FI 883757 A ,B,	16-02-1989
		GR 3020372 T3	30-09-1996
		HK 39595 A	24-03-1995
		HU 47935 A2	28-04-1989
		HU 210815 B3	28-08-1995
		IE 65551 B1	01-11-1995
		IL 87434 A	10-06-1993
		JP 1068373 A	14-03-1989
		JP 1930741 C	12-05-1995
		JP 6062623 B	17-08-1994
		JP 2071105 C	10-07-1996
		JP 3115284 A	16-05-1991
		JP 7113025 B	06-12-1995
		KR 9602849 B1	27-02-1996
		KR 9604940 B1	18-04-1996
		LT 2063 R3	15-06-1993
		LU 88746 A9	04-10-1996
		MC 1968 A	29-09-1989
		MX 9203418 A1	01-07-1992
		NO 883612 A ,B,	16-02-1989
		NZ 225809 A	26-07-1991
		PH 29942 A	16-09-1996
		PH 29943 A	16-09-1996
		PL 274215 A1	19-02-1990
		PT 88261 A ,B	30-06-1989
		SG 9590337 A2	01-09-1995
		SU 1634138 A3	07-03-1991
		ZA 8805995 A	25-04-1990
WO 03041647 A	22-05-2003	WO 03041647 A2	22-05-2003
		US 2003153757 A1	14-08-2003
		WO 03022209 A2	20-03-2003
		US 2003114470 A1	19-06-2003